REAL PARTY IN INTEREST

The real party in interest is Schering AG, as evidenced by the assignment recorded at Reel 012093/Frame 0500.

RELATED APPEALS AND INTERFERENCES

There are no known related appeals or interferences.

STATUS OF CLAIMS

Claims 1, 6, 9 and 17 are cancelled.

Claims 2-5, 7, 8, 10-16 and 18-23 are pending in the present application.

Claim 8, 12 and 21 are withdrawn from consideration.

Claims 2-5, 7, 10, 11, 13-16, 18-20, 22 and 23 are rejected.

Claims 2-5, 7, 10, 11, 13-16, 18-20, 22 and 23 are on appeal.

STATUS OF AMENDMENTS

No amendments were filed after final.

SUMMARY OF CLAIMED SUBJECT MATTER

Appellants' inventions claimed in independent claims 2 and 22 are directed to a combination containing a gestagen of formula I as specified in the claims and a β-cyclodextrin or γ-cyclodextrin or a derivative of β-cyclodextrin or γ-cyclodextrin, which is obtained by etherification or esterification of free alcoholic functions of cyclodextrin. See page 1, first paragraph, page 2, second and third full paragraphs and page 3-5. In claim 2, the open term "comprising" is used, and in claim 22, the closed term "consisting of" is used.

The invention claimed in claim 23 relates to a method of stabilizing the gestagen since in the combination as claimed, for example, in claim 2, the gestagen is stabilized from, for example, acyloin rearrangement. See page 1, first paragraph, page 2, second and third full paragraphs and page 3-5.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The grounds for rejections are under 35 U.S.C. § 103, and are whether the rejected claims are unpatetable as being obvious in view of Schollkopf et al., WO 96/20209, in combination with Backensfeld et al., US 5,798,338, and Hedges, Chem. Rev., 1998.

ARGUMENT

Rejection of Claims 2-5, 7, 10, 11, 13-16, 18-20 and 22

Schollkopf et al. broadly teaches compounds that include compounds of formula I, which are 14,17-C_2 bridged gestagens, but does not teach or suggest their combination with a β-cyclodextrin or γ-cyclodextrin or a derivative of β-cyclodextrin or γ-cyclodextrin (cyclodexrins hereinafter). This is admitted in the Office Action dated December 16, 2004, on page 4, lines 3-4.

Backensfeld et al. relates to compositions for reducing oxidative degradation of 17-α-ethinylestradiol (see the title of the reference and example 1) comprising cyclodextrin and estradiol. This reference does not disclose complexes of a 14,17-C_2 bridged gestagen and a cyclodextrin. Backensfeld et al. teaches a large number of possible sex hormones. See column 1, line 34 to column 2, line 4. Gestagens are also mentioned among the possible sex hormones, and, as examples, at column 1, lines 47-49 of Backensfeld et al. more specifically mention norethisterone, levonorgestrel, gestodene, desorgestrel, and 3-ketodesorgestrel. None of these gestagens possess a 14,17-C_2 bridge.

The gestagens of Backensfeld et al. are different from the claimed gestagens. The gestagens of Backensfeld et al. have a β-hydroxy group, an α-hydrogen atom, or an α-ethinyl group at position 17. The claimed gestagens have a C2-bridge that extends to the C14-atom, and have an α-hydroxyketone side chain at the 17 position. This α-hydroxy side chain of the gestagens in the claimed combination gives rise to an acyloin rearrangement when the claimed gestagens are stored (see page 1, lines 20-23 of the specification). Thus, complexing the gestagen with cyclodextrin stabilizes the gestagen and prevents degradation of the gestagen via acyloin rearrangements. (The cited reference discloses reducing oxidative degradation of estradiols.)

Backensfeld et al. provide no teaching or suggestion to motivate the skilled artisan to stabilize gestagens with a 14,17-C_2 bridge or a 17-(α-hydroxyketone) side chain to prevent/reduce acyloin rearrangements of the gestagen. Further, the skilled artisan, upon

reading Backensfeld et al., would not expect that a composition for reducing oxidative degradation comprising a cyclodextrin and an estradiol (or a gestagen with a 17-β-hydroxy, a 17-α-hydrogen atom, or a 17-α-ethinyl group) would also stabilize a gestagen with a 14,17-C_2 bridge or a 17-α-hydroxyketone side chain to prevent/reduce degradation via acyloin rearrangements of the gestagen.

In sum, Schollkopf et al. teaches compounds which include compounds of formula I of the claims. This reference does not provide any teaching or suggestion for the addition of cyclodextrins. Backensfeld et al. teaches the possibility of using cyclodextrins with estrogens. However, this says nothing with regard to the effect of cyclodextrins on gestagens with a hydroxyketone side chain. Thus, there is no motivation for the claimed combination.

Hedges is cited as an additional reference teaching various advantages and general uses of cyclodextrins, including in pharmaceutical compositions, and methods for processing them, etc. This reference adds nothing more than general broad teachings that are either very broad and removed from the specific invention claimed in this application or are cumulative at most to what the first two references teach.

Although not necessary, appellants submitted data demonstrating the effect of β-cyclodextrin on the degradation of a compound (ZK 187226) according to the invention in a declaration signed on October 25, 2004, and submitted on November 4, 2004. In the control HPLC chromatogram where ZK 187226 is in a tablet without β-cyclodextrin, peaks for the acyloin rearranged degradation byproducts identified by compound numbers in the declaration are also present, whereas in the chromatogram where the ZK 187226 is in a tablet with β-cyclodextrin, no peaks are present for the acyloin rearranged degradation byproducts. This data in that declaration was not quantified by setting forth how much of the ZK 187226 ends up as acyloin rearranged products. Nevertheless, the data clearly established that without the presence of cyclodextrins, acyloin rearrangement takes place, while when cyclodextrins are present, no acyloin rearrangement takes place. This could not have been expected from the teachings of the prior art.

Appellants also submitted additional data in the reply filed on June 16, 2005. Although at the time the data was not in the form of a Declaration, the Examiner in the Office Action dated September 1, 2005, indicated on page 2, lines 4-5 from the bottom of the page that the data have been reviewed. Comments on the data are provided on pages 2 and 3 of said Office Action. A signed declaration referring to this data from said reply is included in

the evidence appendix of this Appeal Brief. Appellants request that the Board consider this data too in the disposition of this case as it is clear that the Examiner also considered this data even though at the time such data was not in the form of a declaration.

The first table in the reply filed on June 16, 2005 demonstrates that the compound ZK 187226, without it being combined with excipients for tabletting, is stable. That is, no substantial degradation is present. One of ordinary skill in the art in view of such data would have lacked the motivation to combine ZK 187226 with compounds taught to stabilize gestagens since this gestagen on its own is stable. One of ordinary skill in the art prior to even trying to stabilize ZK 187226, would have checked whether ZK 187226 needs to be stabilized. Since ZK 187226 is stable, the rejection presents no motivation that would lead one of ordinary skill in the art to combine ZK 187226 with a cyclodextrin as claimed.

The Office Action dated September 1, 2005, requests a similar comparison for the 17-α-ethinylestradiol of Backensfeld et al. The Office Action speculates that "it could very well be that it is the presence of the excipient(s) is the catalyst for oxidative degradation." However, this is merely speculation without basis in the prior art. One of ordinary skill in the art is taught by Backensfeld et al. that the active ingredient, 17-α-ethinylestradiol, and also sex hormones generally go through oxidative degradation reactions. Additionally, nowhere does Backensfeld et al. teach or suggest that these compounds would behave differently when in combination with excipients than when not in combination with excipients.

The second table in the reply filed on June 16, 2005 demonstrates that once ZK 187226 is combined with common excipients (and without cyclodextrins), it degrades due to acyloin rearrangement. See also specification on pages 1 and 2. The data for this second table are calculations of percentages of the decomposition products from the data curves already submitted in graphical format in the previous declaration discussed above. Two groups of decomposition products are calculated in addition to the amount of ZK 187226. The first group constitutes compounds that have a retention time between 3 and 13 minutes, the structure of which compounds is unknown, and the second group is the sum of ZK 187225, ZK 187929, and ZK 187928, which are decomposition products known to be due to acyloin rearrangement of ZK 187226.

As noted above, the structure of the compounds with a retention time between 3 and 13 minutes is unknown. However, ZK 187226, when, by itself, does not decompose to these products as demonstrated in the first table. In any event, one of ordinary skill in the art seeing

from the second table that at least a large part of the degradation is due to acyloin rearrangement of the gestagen ZK 187226, would not have been motivated to combine the same with a cyclodextrin taught to affect degradation due to oxidation, but would have searched for a solution for stabilizing from acyloin rearrangement.

The third table in the reply filed on June 16, 2005 demonstrates significant stabilization of ZK 187226 from acyloin rearrangement in a tablet when combined with cyclodextrins. This significant reduction in acyloin rearrangement of ZK 187226 is unexpected from the prior art, and thus, supports patentablity of the claimed invention.

Rejection of Claim 23

Additionally, independent claim 23 drawn to a method for stabilization of a gestagen from acyloin rearrangement is not taught or suggested by the prior art as this problem was not even recognized by the prior art.

Reversal of the rejection is respectfully and courteously requested.

Respectfully submitted,

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Brion P. Heaney (Reg. No. 32,542)
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Attorney Docket No.: Sch-108

Date: October 11, 2006

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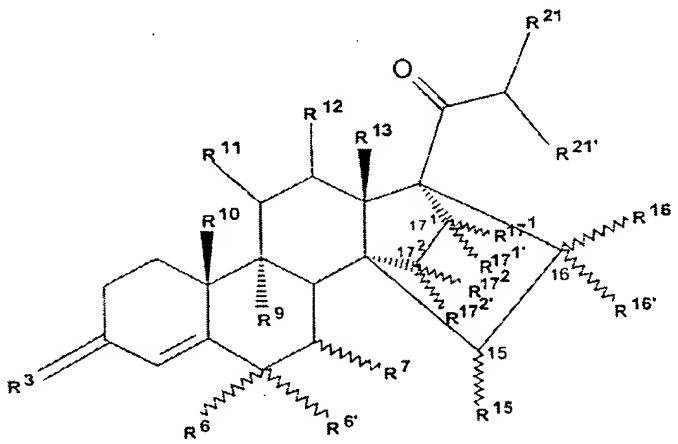
CLAIMS APPENDIX

2. A combination comprising at least one gestagen and a β-cyclodextrin or γ-cyclodextrin or a derivative of β-cyclodextrin or γ-cyclodextrin, which is obtained by etherification or esterification of free alcoholic functions of cyclodextrin, wherein said at least one gestagen is a compound of formula I:



(I)

in which

R^3 is an oxygen atom, a hydroxyimino group, or two hydrogen atoms,

R^6 is a hydrogen, fluorine, chlorine or bromine atom or an α- or β-position C_1-C_4 alkyl radical,
wherein $R^{6'}$ and R^7 represent hydrogen atoms, or else

$R^{6'}$ is a hydrogen, fluorine, chlorine or bromine atom or a C_1-C_4 alkyl radical, wherein $R^{6'}$ and R^7 represent a common additional bond,

R^7 is an α- or β-position C_1-C_4 alkyl radical, wherein R^6 and $R^{6'}$ represent hydrogen atoms, or else

R^6 and R^7 together stand for an α- or β-position methylene group, and $R^{6'}$ is a hydrogen atom, or R^6 and $R^{6'}$ together stand for an ethylene group or a methylene group, and R^7 is a hydrogen atom,

R^9 and R^{10} in each case stand for a hydrogen atom or a common bond,

R^{11} and R^{12} in each case stand for a hydrogen atom or a common bond,

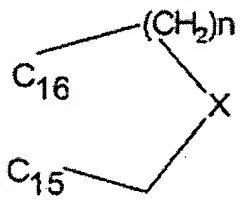
R^{13} is a methyl or ethyl group,

R^{15} is a hydrogen atom or a C_1-C_3 alkyl radical,

R^{16} and $R^{16'}$, independently of one another, stand for a hydrogen atom, a C_1-C_3 alkyl radical or a C_2-C_4 alkenyl radical or together for a C_1-C_3 alkylidene group,

R^{15} and R^{16} stand for a common bond, and $R^{16'}$ stands for a hydrogen atom or a C_1-C_3 alkyl radical, or

R^{15} and R^{16} together stand for a ring of partial formula



in which n = 1 and 2, and X means a methylene group or an oxygen atom, and $R^{16'}$ stands for a hydrogen atom,

R^{17^1} is a hydrogen atom or a C_1-C_3 alkyl radical,

R^{17^2} is a hydrogen atom, a C_1-C_3 alkyl radical, or a C_2-C_4 alkenyl radical,

$R^{17^{1'}}$ and $R^{17^{2'}}$ in each case is a hydrogen atom or for a common bond,

R^{21} is a hydrogen atom or a C_1-C_3 alkyl radical,

$R^{21'}$ is a hydroxy group.

3. The combination according to claim 2, wherein the gestagen is a (21S)-21-hydroxy-21-methyl-14,17-ethano-19-norpregna-4,9,15-triene-3,20-dione.

4. The combination according to claim 2, wherein the cyclodextrin is a β-cyclodextrin.

5. The combination according to claim 2, wherein the cyclodextrin and the gestagen are present as a β-cyclodextrin complex having a gestagen : cyclodextrin molar ratio of 1:n, with

n greater than or equal to 1, or are present as a γ-cyclodextrin complex having a gestagen : cyclodextrin molar ratio of 1:n, with n greater than or equal to 1.

7. The combination according to claim 2 which has been formulated as a stable, oral formulation.

10. A pharmaceutical composition comprising a combination according to claim 2 and a pharmaceutically acceptable adjuvant or vehicle.

11. The pharmaceutical composition of claim 10 which has been formulated for peroral, oral, parenteral, transdermal, pulmonary, nasal, rectal, vaginal or intrauterine use.

13. A method for birth control comprising administering to a patient in need thereof a composition according to claim 10.

14. A method for stabilization of a gestagen of claim 2 comprising mixing said gestagen with a β-cyclodextrin or a γ-cyclodextrin or a derivative of a β-cyclodextrin or a γ-cyclodextrin, which is obtained by etherification or esterification of free alcoholic functions of cyclodextrins.

15. A method for complexing a gestagen according to claim 2 and a β-cyclodextrin or a γ-cyclodextrin comprising triturating said gestagen and said cyclodextrin to form a dry mixture of the gestagen-cyclodextrin complex, or combining a solution of said gestagen with a solution of said β-cyclodextrin or said γ-cyclodextrin to induce precipitation.

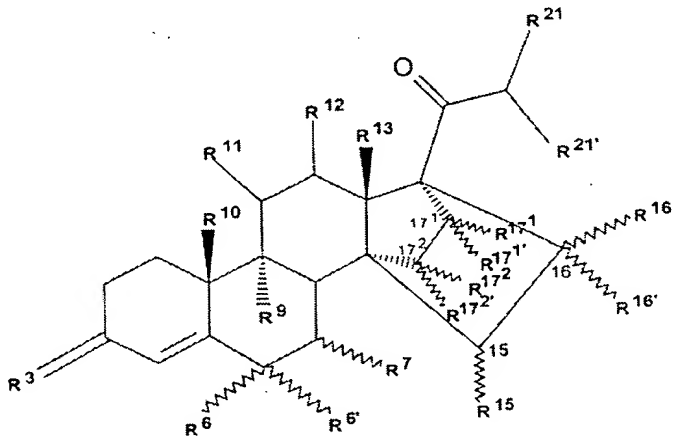
16. A method for direct pelletizing of a gestagen complex according to claim 2 with a β-cyclodextrin or a γ-cyclodextrin and a pharmaceutically compatible adjuvant comprising mixing said gestagen, cyclodextrin and said adjuvant to form a gestagen-cyclodextrin-adjuvant complex and pelleting the gestagen-cyclodextrin-adjuvant complex.

18. The process of claim 15, wherein precipitating is co-precipitating.

19. A process for complexing a gestagen according to claim 2 and a β-cyclodextrin or a γ-cyclodextrin comprising adding an ethanolic solution of said gestagen to an aqueous solution of said cyclodextrin to form a precipitate of the gestagen-cyclodextrin complex.

20. The combination according to claim 2, wherein the gestagen is a (21S)-21-hydroxy-21-methyl-14,17-ethano-19-norpregna-4,9,15-triene-3,20-dione and the cyclodextrin is a β-cyclodextrin.

22. A combination consisting of a gestagen and a β-cyclodextrin or a γ-cyclodextrin or a derivative of β-cyclodextrin or a γ-cyclodextrin, which is obtained by etherification or esterification of free alcoholic functions of a cyclodextrin, wherein said at least one gestagen is a compound of formula I:



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in which

R^3 stands for an oxygen atom, the hydroxyimino group, or two hydrogen atoms,

R^6 stands for a hydrogen, fluorine, chlorine or bromine atom or for an α- or β-position C_1-C_4 alkyl radical,
wherein then $R^{6'}$ and R^7 represent hydrogen atoms, or else

$R^{6'}$ stands for a hydrogen, fluorine, chlorine or bromine atom or for a C_1-C_4 alkyl radical, wherein then $R^{6'}$ and R^7 represent a common additional bond,

R^7 stands for an α- or β-position C_1-C_4 alkyl radical, wherein then R^6 and $R^{6'}$ represent hydrogen atoms, or else

R^6 and R^7 together stand for an α- or β-position methylene group, and $R^{6'}$ stands for a hydrogen atom, or R^6 and $R^{6'}$ together stand for an ethylene group or a methylene group, and R^7 stands for a hydrogen atom,

R^9 and R^{10} in each case stand for a hydrogen atom or a common bond,

R^{11} and R^{12} in each case stand for a hydrogen atom or a common bond,

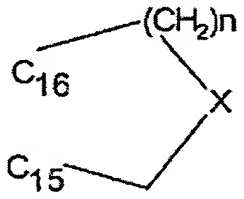
R^{13} stands for a methyl or ethyl group,

R^{15} stands for a hydrogen atom or a C_1-C_3 alkyl radical,

R^{16} and $R^{16'}$, independently of one another, stand for a hydrogen atom, a C_1-C_3 alkyl radical or a C_2-C_4 alkenyl radical or together for a C_1-C_3 alkylidene group,

R^{15} and R^{16} stand for a common bond, and $R^{16'}$ stands for a hydrogen atom or a C_1-C_3 alkyl radical, or

R^{15} and R^{16} together stand for a ring of partial formula



in which n = 1 and 2, and X means a methylene group or an oxygen atom, and $R^{16'}$ stands for a hydrogen atom,

R^{17^1} stands for a hydrogen atom or a C_1-C_3 alkyl radical,

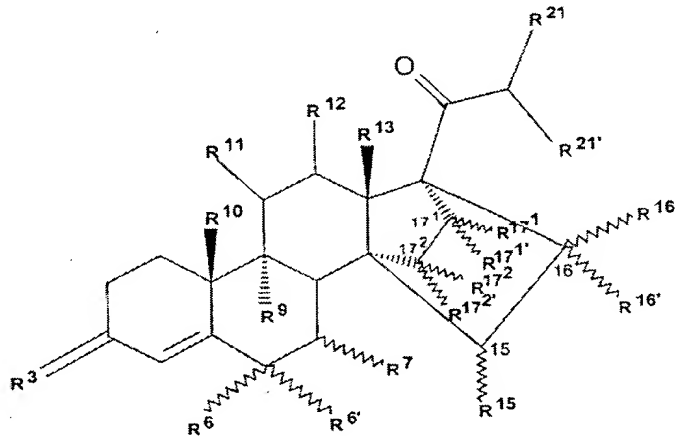
R^{17^2} stands for a hydrogen atom, a C_1-C_3 alkyl radical, or a C_2-C_4 alkenyl radical,

$R^{17^{1'}}$ and $R^{17^{2'}}$ in each case stand for a hydrogen atom or for a common bond,

R^{21} stands for a hydrogen atom or a C_1-C_3 alkyl radical,

$R^{21'}$ stands for a hydroxy group.

23. A method for stabilization of a gestagen from acyloin rearrangement comprising mixing said gestagen with a β-cyclodextrin or a γ-cyclodextrin or a derivative of a β-cyclodextrin or a γ-cyclodextrin, which is obtained by etherification or esterification of free alcoholic functions of cyclodextrins, wherein said gestagen is a compound of formula I:



(I)

in which

R^3 is an oxygen atom, a hydroxyimino group, or two hydrogen atoms,

R^6 is a hydrogen, fluorine, chlorine or bromine atom or an α- or β-position C_1-C_4 alkyl radical,
wherein $R^{6'}$ and R^7 represent hydrogen atoms, or else

$R^{6'}$ is a hydrogen, fluorine, chlorine or bromine atom or a C_1-C_4 alkyl radical, wherein $R^{6'}$ and R^7 represent a common additional bond,

R^7 is an α- or β-position C_1-C_4 alkyl radical, wherein R^6 and $R^{6'}$ represent hydrogen atoms, or else

R^6 and R^7 together stand for an α- or β-position methylene group, and $R^{6'}$ is a hydrogen atom, or R^6 and $R^{6'}$ together stand for an ethylene group or a methylene group, and R^7 is a hydrogen atom,

R^9 and R^{10} in each case stand for a hydrogen atom or a common bond,

R^{11} and R^{12} in each case stand for a hydrogen atom or a common bond,

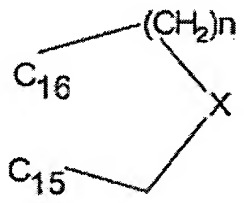
R^{13} is a methyl or ethyl group,

R^{15} is a hydrogen atom or a C_1-C_3 alkyl radical,

R^{16} and $R^{16'}$, independently of one another, stand for a hydrogen atom, a C_1-C_3 alkyl radical or a C_2-C_4 alkenyl radical or together for a C_1-C_3 alkylidene group,

R^{15} and R^{16} stand for a common bond, and $R^{16'}$ stands for a hydrogen atom or a C_1-C_3 alkyl radical, or

R^{15} and R^{16} together stand for a ring of partial formula



in which n = 1 and 2, and X means a methylene group or an oxygen atom, and $R^{16'}$ stands for a hydrogen atom,

R^{17^1} is a hydrogen atom or a C_1-C_3 alkyl radical,

R^{17^2} is a hydrogen atom, a C_1-C_3 alkyl radical, or a C_2-C_4 alkenyl radical,

$R^{17^{1'}}$ and $R^{17^{2'}}$ in each case is a hydrogen atom or for a common bond,

R^{21} is a hydrogen atom or a C_1-C_3 alkyl radical,

$R^{21'}$ is a hydroxy group.

EVIDENCE APPENDIX

Declaration dated May 31, 2006, signed by Thomas Backensfeld follows on the next two pages labeled as pages 14A and 14B in the lower right hand corner.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	:	09/807,402
Applicant	:	Hofert et al.
Filed	:	August 3, 2001
Title	:	COMBINATION OF GESTAGENS AND SUGARS
TC/A.U.	:	1623
Examiner	:	L. C. Maier

DECLARATION UNDER 37 C.F.R. §1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Thomas Backensfeld, being duly warned, declare that:

I am a listed inventor of the above-captioned application and am, therefore, familiar with the invention described therein and with the grounds for rejection made against the claims of the application in all of the Office Actions from the U.S. Patent and Trademark Office (USPTO hereinafter).

My expertise for making this declaration is demonstrated in the CV attached to the declaration filed on November 4, 2004.

If a patent issues from this application and if it is decided by the assignee to pursue a commercial product falling under its claims and if such a commercial product is approved by FDA and sold in the US, then under German law, I and the other inventors will receive some income derived from such sales.

The data presented to the USPTO in the Reply filed on June 16, 2005 and discussion thereof from said Reply, including the material starting on page 10, third full paragraph, after the heading "Rejections Under 35 U.S.C. § 103" to page 12, the end of the table on said page, are incorporated herein by reference in their entirety.

I declare that the data incorporated herein are the result of experiments that were conducted by me or under my supervision and that I am in complete agreement with the comments about the data in said reply.

Based on the data in the first table, one of ordinary skill in the art would have lacked the motivation to combine ZK 187226 with compounds taught to stabilize gestagens since this gestagen on its own is stable. One of ordinary skill in the art prior to even trying to

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stabilize ZK 187226, would have checked whether ZK 187226 needs to be stabilized. Since ZK 187226 is stable, there is no motivation that would lead one of ordinary skill in the art to combine ZK 187226 with a cyclodextrin as claimed.

The second table demonstrates that once ZK 187226 is combined with common excipients (and without cyclodextrins), it degrades due to acyloin rearrangement. The data for this second table are calculations of percentages of the decomposition products from the data curves already submitted in graphical format in the previous declaration. Two groups of decomposition products are calculated in addition to the amount of ZK 187226. The first group constitutes compounds that have a retention time between 3 and 13 minutes, the structure of which compounds is unknown, and the second group is the sum of ZK 187225, ZK 187929, and ZK 187928, which are decomposition products known to be due to acyloin rearrangement of ZK 187226. The structure of the compounds with a retention time between 3 and 13 minutes is unknown. However, ZK 187226, when, by itself, does not decompose to these products as demonstrated in the first table. One of ordinary skill in the art seeing from the second table that at least a large part of the degradation is due to acyloin rearrangement of the gestagen ZK 187226, would not have been motivated to combine the same with a cyclodextrin taught to affect degradation due to oxidation.

The third table demonstrates significant stabilization of ZK 187226 from acyloin rearrangement in a tablet when combined with cyclodextrins. This significant reduction in acyloin rearrangement of ZK 187226 is unexpected from the prior art, and thus, supports patentablity of the claimed invention.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

31.05.2006

Thomas Backensfeld Date

14B

RELATED PROCEEDINGS APPENDIX

NONE